

## **Updating the Guideline Methodology of the Healthcare Infection Control Practices Advisory Committee (HICPAC)**

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**Acknowledgement**

The Healthcare Infection Control Practices Advisory Committee acknowledges the following individuals for their critical input in the methodology update: Carolyn V. Gould, MD, MSCR; David A. Pegues, MD; Taranisa MacCannell, MSc, PhD; Ingi Lee, MD, MSCE; Kurt B. Stevenson, MD, MPH; Gretchen Kuntz, MSW, MSLIS; Michael R. Bell, MD.

**Disclosure of Financial Interests and Relationships**

The authors C.A.U., R.K.A., and P.J.B report no actual or potential conflicts of interest. C.A.U. and R.K.A. received funding from the CDC to support the guideline development process.

**Disclaimer**

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

## **Background**

The Healthcare Infection Control Practices Advisory Committee (HICPAC) is a federal advisory committee made up of 14 external infection control and public health experts who provide guidance to the Centers for Disease Control and Prevention (CDC) and the Secretary of the Department of Health and Human Services (DHHS) regarding the practice of healthcare infection prevention and control, strategies for surveillance, and prevention and control of healthcare associated infections (HAIs) in United States healthcare facilities. As such, one of the primary functions of the committee is to issue recommendations for preventing and controlling HAIs in the form of guidelines and less formal communications.<sup>1, 2</sup> Currently, HICPAC guidance documents are available on its website for download<sup>1</sup>, and a number of additional documents have been published since HICPAC's inception, most commonly in *Morbidity and Mortality Weekly Report (MMWR)*, *Infection Control and Hospital Epidemiology (ICHE)*, and the *American Journal of Infection Control (AJIC)*.

The strength of the HICPAC guidance documents stem from their process of development as well as their content and organization. HICPAC's processes were set in motion at the time of its creation by the Secretary of DHHS in 1991. The committee was organized at the request of CDC to provide a setting for guideline development that was free from political or financial influence and that enabled multidisciplinary and public input. Members are recommended by CDC and appointed by the Secretary of DHHS from experts in the fields of infectious diseases, healthcare associated infections, nursing, surgery, epidemiology, public health, health outcomes and related areas of expertise. In fact, the Federal Advisory Committee Act mandates that membership include individuals with a variety of interests, backgrounds and expertise. All HICPAC

members are required to regularly disclose potential conflicts of interest. The committee also has ex officio members like the Agency for Healthcare Research and Quality as well as liaisons from professional organizations like the Association for Professionals in Infection Control and Epidemiology Inc., and the Society for Healthcare Epidemiology of America. Other such non-voting representatives are included as the Secretary deems necessary to carry out the functions of the Committee effectively. Since the creation of HICPAC, guidelines have been drafted by CDC in collaboration with outside experts, reviewed and revised within HICPAC, and published in the Federal Register for public comment before final publication.<sup>1-3</sup>

The content and organization of HICPAC's guidance documents include: 1) a thorough yet concise review of the guideline topic and 2) a recommendations section which communicates strength of recommendations as well as supporting evidence grades. This structure has enabled the committee to differentiate those practices for which the available scientific evidence provides strong support or rejection (Category I) from those practices where there is only suggestive or less definitive evidence (Category II). The grading of the evidence behind the recommendation has also allowed the committee to differentiate strong recommendations with a firm scientific foundation (Category IA) from strong recommendations with a weaker scientific foundation (Category IB). The more recent introduction of Category IC recommendations has enabled a further distinction of strong recommendations mandated by federal and/or state statutes, regulations or standards.

The value of HICPAC documents is reflected in their use by individual infection preventionists and healthcare epidemiologists <sup>4</sup>, as well as national societies committed to infection prevention and control<sup>5</sup>. In addition, the value of HICPAC documents is reflected in a growing body of evidence suggesting they enhance the quality and safety of patient care <sup>6-10</sup>. For example, Manangan and others demonstrated an association between a high level of awareness and adoption of HICPAC recommendations with a decrease in the incidence of ventilator-associated pneumonia (VAP) among 188 hospitals.<sup>10</sup> Likewise, almost 90% of direct care providers were aware of recommendations in CDC's Hand Hygiene Guideline, and increased adherence with these recommendations correlated with a lower incidence of central line-associated bloodstream infections (CLABSI).<sup>7</sup> Several other recent investigations have provided indirect evidence that HICPAC recommendations applied in “bundles” can result in significant reductions in the incidence of CLABSI.<sup>6, 8, 9</sup>

### **Strengthening HICPAC Guidelines to Address Emerging Needs**

Despite the strengths of HICPAC's guidance documents and the processes used in their development, a number of recent advances in guideline development and implementation have emerged that offer HICPAC an opportunity to further strengthen the validity and impact of their guidelines. Many of these advances have been integrated into the guideline development processes of societies on the forefront of guideline development, providing HICPAC with excellent models for updating its guideline methodology.<sup>11-16</sup> Advances in guideline development and implementation have also been promoted by authors, committees, and organizations focused on improving the validity and usability of guidelines.<sup>17-21</sup>

Importantly, these advances also allow HICPAC to address emerging challenges in guideline development in the area of infection prevention and control. Such challenges include: 1) an immense and rapidly growing evidence base that makes it more important than ever to utilize strategies that allow one to efficiently locate and use the most valid and clinically relevant studies available; 2) emerging infections for which infection preventionists require guidance yet for which there is little evidence on which to base recommendations; 3) increasing attention to infection prevention and control by surveyors, regulatory agencies, government and commercial payors in the United States and abroad, making the need for rigorous evidence-based guidelines more pressing<sup>22, 23</sup>; and 4) escalating quantity of guidelines available to guide care on any given topic, which makes clear communication, recommendation bundles, and implementation plans key to any guideline's success<sup>24, 25</sup>. In addition, the threats of commercial and political bias are as important now as they were at the time HICPAC was created, particularly with the potential financial benefits to industry of guideline endorsements<sup>21, 26</sup>, and the challenge that payors and healthcare facilities have to improve the value of their healthcare dollar.

Given these challenges, the needs of HICPAC are clear. The committee must:

- 1) create the processes necessary to rapidly develop and update guidelines to allow an appropriate response to emerging needs and new scientific evidence;
- 2) address the key clinical questions of infection preventionists and providers in a targeted way;
- 3) use the best available evidence to answer those questions efficiently;
- 4) provide transparent recommendations without bias; and
- 5) prioritize recommendations for implementation.

This document provides an update on the methods used by HICPAC to address these



needs. Specifically, we describe how HICPAC is using emerging methods in guideline development to create guidelines based on targeted systematic reviews of the best available evidence, with explicit links between the evidence and recommendations, which can be efficiently updated and provide priorities for practitioners as well as future research agendas. We also discuss methods used to enhance the reach and impact of these guidelines on the quality, safety and value of patient care. These methodologies are approved by HICPAC and will be used for subsequent guidelines issued by HICPAC, beginning with the Prevention of Catheter Associated Urinary Tract Infection Guideline, which was initiated in the Fall of 2007.

### **Organizing to Accomplish Our Goals**

In order to reengineer its guideline development process, HICPAC first restructured its approach. In its new approach, each guideline is developed by a working group in consultation with a panel of content experts and HICPAC (*Figure 1*). All funding is provided by CDC. Financial conflicts of interest are vetted and disclosed for all working group, content experts, and HICPAC members.

The working group has accountability for all phases of methodology, including development of the key questions around which the guideline is based, the systematic review of the evidence, and the guideline itself. It also is responsible for providing content experts and HICPAC members with progress updates at agreed-upon dates. Each working group includes but is not limited to three main stakeholders: a HICPAC member, a staff member from CDC, and outside experts in the methodology of guideline development. Each member has individual as well as overlapping accountabilities.

The HICPAC member is responsible for helping to develop the key questions, reviewing abstracts and full text articles for inclusion in the guideline, reviewing summaries of the evidence and the guideline recommendations, and communicating progress of the working group at regular HICPAC meetings, as well as communicating progress to and soliciting input from experts who are external to HICPAC.

The CDC staff member comes from the Division of Healthcare Quality Promotion in the National Center for Preparedness, Detection and Control of Infectious Diseases, and responsibilities include helping to develop key questions, reviewing abstracts and full text for inclusion, and writing the evidence summaries and recommendations as well as the following guideline sections: the executive summary, summary of recommendations, implementation and audit, recommendations for further research and background.

The experts in guideline methodology include a project manager, an analyst, and a medical librarian. The role of the project manager includes developing and maintaining guideline methods, setting the timeline, and reviewing and integrating all aspects of guideline development. The analyst extracts data from included studies, builds evidence tables, and grades the overall quality of the evidence for guideline questions using formal processes. The librarian assists the working group in developing search strategies and choosing resources to find relevant references, run searches, and manage included and excluded references.

The panel of content experts consists of three or more content experts both internal and external to HICPAC. These experts are chosen at the discretion of HICPAC. The expert panel participates and provides feedback in regular progress

updates, and provides in-depth reviews of key questions, the bibliography resulting from the initial literature search, the draft evidence report, and guideline recommendations.

HICPAC members and liaisons participate in the guideline development process and provide feedback in regular progress updates, as well as on the draft evidence report and guideline recommendations. HICPAC members then vote to approve the final guideline.

The expertise and experience of relevant professional societies is also critical to this process. As such, representatives of these societies can participate through multiple routes, including as HICPAC liaisons, content experts, or working group members.

## **Methods in Guideline Development**

HICPAC guidelines are now based on targeted systematic reviews of the best available evidence. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach is used to provide explicit links between the available evidence and the resulting recommendations.<sup>27-30</sup> The guideline development process is outlined in *Figure 2*.

### **Development of Key Questions**

Each HICPAC guideline begins with the drafting and refining of the key questions most critical to infection prevention and control personnel and providers for the given guideline topic. These questions then serve as a foundation for the guideline, and guide the systematic review of the evidence and the development of the guideline recommendations. To develop the key questions, the working group first conducts a search of medical literature databases and websites for all relevant guidelines and

narrative reviews on the topic of interest, and then drafts key questions based on their review of these documents. Databases commonly searched include MEDLINE and the National Guideline Clearinghouse. Websites commonly searched include those of government technology assessment programs like the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom <sup>31</sup>, commercial payors like BlueCross/BlueShield in the United States <sup>32</sup>, or federal or state websites in the United States. Once a preliminary list of key questions is developed from an examination of the relevant guidelines and reviews identified in the search, the key questions are vetted and revised by the content experts, and then are presented to and finalized by HICPAC members.

### **Literature Search**

Following the development of the key questions, search terms are developed for identifying the literature most relevant to those questions. For the purposes of quality assurance, these terms are compared to those used in relevant guidelines, reviews and seminal studies. These search terms are then incorporated into search strategies for the relevant electronic medical literature databases. Searches are commonly performed in MEDLINE, EMBASE, CINAHL and Cochrane, and the resulting references are imported into reference management software, where duplicates can be resolved. Cochrane reviews ultimately included in guidelines are checked for updates prior to completion of the first guideline draft.

### **Study Selection**

In general, a best available evidence approach is used to review articles for inclusion. For example, if there are randomized controlled trials (RCTs) that address a

therapy question, then evidence lower in the evidence hierarchy may not be considered. Inclusion and exclusion criteria that are general or specific to individual key questions are developed and used to review references, starting with titles and abstracts. Full text articles are reviewed using the same criteria and are retrieved if they meet inclusion criteria. Studies that are commonly included are those that are: 1) relevant to one or more key questions, 2) primary analytic research, a systematic review or meta-analysis, and 3) written in English. Disagreements between reviewers regarding whether an individual study meets inclusion/exclusion criteria are resolved by consensus of those reviewers.

### **Data Extraction and Synthesis**

For those studies meeting inclusion criteria, data relevant to the evidence review and guideline development is extracted into evidence tables. This data commonly includes: the study author, year, design, quality, objective, population, setting, sample size, power, follow-up, and definitions and results of clinically relevant outcomes. Evidence tables are developed for each key question, with study data being extracted into the relevant evidence tables. Then, studies are organized by the common themes that emerge within each evidence table. Data are extracted by one or more authors, and disagreements are resolved by the remaining authors. Data and analyses are most often extracted as originally presented in the included studies. Meta-analyses are performed only where their use is deemed critical to a recommendation and only in circumstances where multiple studies with sufficiently homogenous populations, interventions, and outcomes can be analyzed. Systematic reviews may also be included in a guideline if there are a large number of relevant reviews available in the literature.<sup>33</sup>

Otherwise, systematic reviews will be used as a source of primary references for the guideline. To ensure that all relevant studies are captured in the search, the bibliography is vetted by the content experts.

## **Grading of Evidence**

First, the quality of each study is assessed using scales adapted from existing methodology checklists<sup>34-38</sup>, and scores are recorded in the evidence tables. Next, the quality of the evidence base is assessed using methods adapted from the GRADE Working Group.<sup>27-30, 39</sup> In summary, GRADE tables are developed for each of the interventions or questions addressed within the evidence tables. Included in the GRADE tables are the intervention of interest, any outcomes listed in the evidence tables that are judged to be clinically important by the working group, the quantity and type of evidence for each outcome, the relevant findings, and the GRADE of evidence for each outcome, as well as an overall GRADE of the evidence base for the given intervention or question. For therapy or harm questions, the initial GRADE of evidence for each outcome is deemed high if the evidence base includes an RCT or a systematic review of RCTs, low if the evidence base includes only observational studies, or very low if the evidence base consists only of descriptive studies (i.e., uncontrolled studies) or expert opinion. The initial GRADE is then modified by eight criteria. Criteria which can decrease the GRADE of an evidence base include poor quality of individual studies, inconsistent findings among studies, indirectness of study findings to the study question, imprecision of study estimates, and publication bias. Criteria that can increase the GRADE include a large magnitude of effect, a dose-response gradient, or inclusion of unmeasured confounders that would increase the effect size (Table 1). For questions

regarding diagnostic measures (e.g., sensitivity or predictive values) or descriptive measures (e.g., prevalence or incidence), the initial GRADE of evidence can be high even if the evidence base only includes descriptive study designs, like cross-sectional studies.<sup>30</sup> The initial GRADE can then be modified by criteria similar to those used for therapy or harm questions. GRADE definitions are as follows<sup>27, 28</sup>:

1. High - further research is very unlikely to change confidence in the estimate of effect
2. Moderate - further research is likely to affect confidence in the estimate of effect and may change the estimate
3. Low - further research is very likely to affect confidence in the estimate of effect and is likely to change the estimate
4. Very low - any estimate of effect is very uncertain

After determining the GRADE of the evidence base for each outcome of a given intervention or question, the overall GRADE of the evidence base for that intervention or question is calculated. The overall GRADE is based on the lowest GRADE for the outcomes deemed critical by the working group to making a recommendation.

### **Formulating Recommendations**

Narrative evidence summaries are then drafted by the working group using the evidence and GRADE tables. One summary is written for each theme that emerges under each key question. The working group then uses the narrative evidence summaries to develop guideline recommendations. Factors determining the strength of a recommendation include<sup>29</sup>: 1) the values and preferences of the working group when determining which study outcomes are critical<sup>28</sup>, 2) the risks and benefits that result

from weighing the critical outcomes, and 3) the overall GRADE of the evidence base for the given intervention or question (Table 2). If weighing the critical outcomes for a given intervention or question results in a "net benefit" or a "net harm", then a Category I Recommendation is formulated to strongly recommend for or against the given intervention respectively. If weighing the critical outcomes for a given intervention or question results in a "trade off" between benefits and harms, then a Category II Recommendation is formulated to recommend that providers or institutions consider the intervention when deemed appropriate. If weighing the critical outcomes for a given intervention or question results in an "uncertain trade off" between benefits and harms, then No Recommendation is formulated to reflect this uncertainty.

For Category I recommendations, levels A and B represent the quality of the evidence underlying the recommendation, with A representing high to moderate quality evidence and B representing low to very low quality evidence but established standards (e.g., aseptic technique, education and training). For Category IB recommendations, although there may be low to very low quality evidence directly supporting the benefits of the intervention, the theoretical benefits are clear, and the theoretical risks are marginal. Category IC represents practices required by state or federal regulation, regardless of the quality of evidence. It is important to note that the strength of a Category IA recommendation is equivalent to that of a Category IB or IC recommendation; it is only the quality of the evidence underlying the Category IA recommendation that makes it different from a Category IB.



In some instances, multiple recommendations may emerge from a single narrative evidence summary. The updated HICPAC categorization scheme for recommendations is provided in Table 3.

Category I recommendations are defined as strong recommendations with the following implications<sup>29</sup>:

1. For patients: Most people in the patient's situation would want the recommended course of action and only a small proportion would not. Patients should request discussion if the intervention is not offered.
2. For clinicians: Most patients should receive the recommended course of action.
3. For policymakers: The recommendation may be considered for policy in many situations.

Category II recommendations are defined as weak recommendations with the following implications<sup>29</sup>:

1. For patients: Most people in the patient's situation would want the recommended course of action, but some may not.
2. For clinicians: Different choices will be appropriate for different patients and clinicians must help patients arrive at management decisions consistent with their values and preferences.
3. For policymakers: Policy making requires substantial debate and involvement of many stakeholders.

Our evidence-based recommendations are then cross-checked with those from guidelines identified in our original systematic search. In addition, recommendations from previous guidelines for topics not directly addressed by our systematic review of

the evidence are included in a "Summary of Recommendations" if they are deemed critical to the target users of the guideline. Unlike recommendations informed by the literature search, these recommendations are not linked to a key question. Instead, these recommendations are agreed upon by expert consensus and are generally designated either Category IB if they represent a strong recommendation based on accepted practices (e.g., aseptic technique) or Category II if they are a suggestion based on a probable net benefit despite limited evidence.

We carefully select the wording of each recommendation to reflect the recommendation's strength.<sup>40</sup> We use the active voice when writing Category I recommendations - the strong recommendations. Phrases like "do" or "do not" and verbs without conditionals are used to convey certainty. A passive voice is used when writing Category II recommendations - the weak recommendations. Words like "consider" and phrases like "is preferable," "is suggested," or "is not suggested" are used to reflect the lesser certainty of the Category II recommendations. Rather than a simple statement of fact, each recommendation is actionable, describing precisely a proposed action to take.<sup>41</sup>

The category "No recommendation/unresolved issue" is most commonly applied to situations where either: 1) the overall quality of the evidence base for a given intervention is low to very low or 2) there is no published evidence on outcomes deemed critical to weighing the risks and benefits of a given intervention. If the latter is the case, those critical outcomes are noted at the end of the relevant evidence summary.

All recommendations are formulated to be consistent with policies from the United States Food and Drug Administration (FDA) and Environmental Protection Agency (EPA). All recommendations are approved by HICPAC members, and focus only on efficacy, effectiveness, and safety. Yet, the optimal use of these guidelines should include a consideration of the costs relevant to the local setting of guideline users.

### **Reviewing and Finalizing the Guideline**

After a draft of the tables, narrative summaries, and recommendations is completed, the working group shares this draft with the content experts for review in depth. While the content experts are reviewing this draft, the working group completes the remaining sections of the guideline, including the executive summary, background, summary of recommendations, and recommendations for guideline implementation, audit, and further research. The working group then makes revisions to the draft based on feedback from the content experts, and presents the entire draft guideline to HICPAC for review. CDC then submits the guideline for clearance, and posts it on the Federal Register for public comment. After a period of public comment, the guideline is revised accordingly, and the final guideline is published and posted on the HICPAC website.

### **Updating the Guideline**

Guidelines will be reassessed periodically, and general or targeted revisions to guidelines will be dictated by new research and technological advancements in the particular area of interest.<sup>42</sup> Reassessments and updates will occur at the request of HICPAC.

## **Guideline Implementation**

To improve the impact of guidelines on patient care quality and safety, multiple implementation initiatives are underway.<sup>5</sup> In addition, future HICPAC guidelines will include an implementation and audit section. This section includes multi-modal implementation of specific recommendations or modules<sup>25</sup> that highlight the most critical recommendations in the guideline.<sup>24</sup> Besides being the focus of infection preventionists and healthcare epidemiologists, these recommendations may also be ripe for integration into computerized clinical decision support systems.<sup>43</sup> This section also includes performance indicators that can be used by healthcare facilities or regulators of such facilities to improve guideline adherence and ultimately patient care, and may be the focus of pay for performance contracts either locally or nationally. These modules and performance indicators established by HICPAC are based on the evidence review and recommendations.

## **Looking to Future Challenges and Opportunities**

By integrating current advances in guideline development and implementation into future HICPAC guidelines, we believe HICPAC will be able to confront many of today's emerging challenges successfully. However, there are a number of methodological challenges that are inadequately addressed by current advances. These challenges will likely be addressed by future advances, and HICPAC will stand at the ready to integrate these future advances into its processes. Some such methodological challenges include: 1) questions for which there is little to no evidence upon which to base a recommendation, there is little to no requirement for evidence given the high prior probability of a recommendation's success<sup>44, 45</sup>, or the evidence

arises from basic science studies whose strength of evidence may not be accurately reflected in the current approaches to grading an evidence base (this last point is particularly relevant to the evidence addressing infection prevention and control questions); 2) those inherent to using systematic reviews in a systematic review, including how to judge the quality of studies included in the original systematic review<sup>33</sup>; 3) how to use meta-analyses in guidelines effectively given the heterogeneity of populations, interventions and outcomes often studied to address a single question; 4) the role of cost analyses in recommendations, particularly given the sometimes great differences in the costs of drugs and devices by state and by healthcare facility<sup>46, 47</sup>; and 5) the use of population based patient preference evidence to inform individual patient decisions<sup>48-51</sup>.

In addition, there are operational challenges that remain despite HICPAC's new approach to guideline development. To maintain the success and efficiency of HICPAC's new approach, the committee may want to rely on a small cadre of HICPAC members and CDC staff trained and experienced in the methods of guideline development; however, this methods expertise must be balanced by content expertise, and this balance may result in a less efficient but more valid guideline development process. Second, guidelines must be developed efficiently and updated regularly if they are to provide the most valid, relevant and up-to-date guidance, particularly in the context of emerging infections for which there may be a rapidly growing body of literature; however, this efficiency can conflict with the time often required for sufficient expert and public input. Third, guideline implementation could be markedly improved with the development of strategies to enable automatic integration of guidelines into

computerized clinical decision support.<sup>43</sup> Fourth, as highlighted by a recent report by the U.S. Government Accountability Office, the quantity of existing HICPAC recommendations is substantial and there is a need to assist providers with translation and prioritization of these recommendations across the continuum of care.<sup>52</sup> Lastly, HICPAC will need to identify gaps in research to better prevent and control infections. In fact, one of the major strengths of performing a systematic review to develop a guideline is the ability to systematically uncover these critical evidence gaps. These gaps often represent only a handful of potential research studies which, if performed, could provide much needed answers to our most critical questions.

## **Conclusion**

The current update to HICPAC's guideline methodology builds on past strengths and current advances in guideline development and implementation, and enables HICPAC to improve the validity and usability of its guidelines while also addressing emerging challenges in guideline development in the area of infection prevention and control. Despite the current update, methodological and operational challenges persist, and HICPAC is ready to integrate any future advances into its processes as appropriate.

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**Table 1: Rating the Quality of Evidence for Therapy or Harm Studies Using the GRADE Approach**

Type of Evidence	Initial Grade	Criteria to Decrease Grade	Criteria to Increase Grade	Overall Quality Grade
RCT	High	<u>Quality</u> Serious (-1 grade) or very serious (-2 grades) limitation to study quality	<u>Strong association</u> Strong (+1 grade) or very strong evidence of association (+2 grades)	High Moderate
Observational study	Low	<u>Consistency</u> Important inconsistency (-1 grade)	<u>Dose-response</u> Evidence of a dose-response gradient (+1 grade)	Low
Any other evidence (e.g., expert opinion)	Very low	<u>Directness</u> Some (-1 grade) or major (-2 grades) uncertainty about directness  <u>Precision</u> Imprecise or sparse data (-1 grade)  <u>Publication bias</u> High risk of bias (-1 grade)	<u>Unmeasured Confounders</u> Inclusion of unmeasured confounders increases the effect size (+1 grade)	Very low

Abbreviations: Grading of Recommendations Assessment, Development and Evaluation (GRADE); Randomized Controlled Trial (RCT).

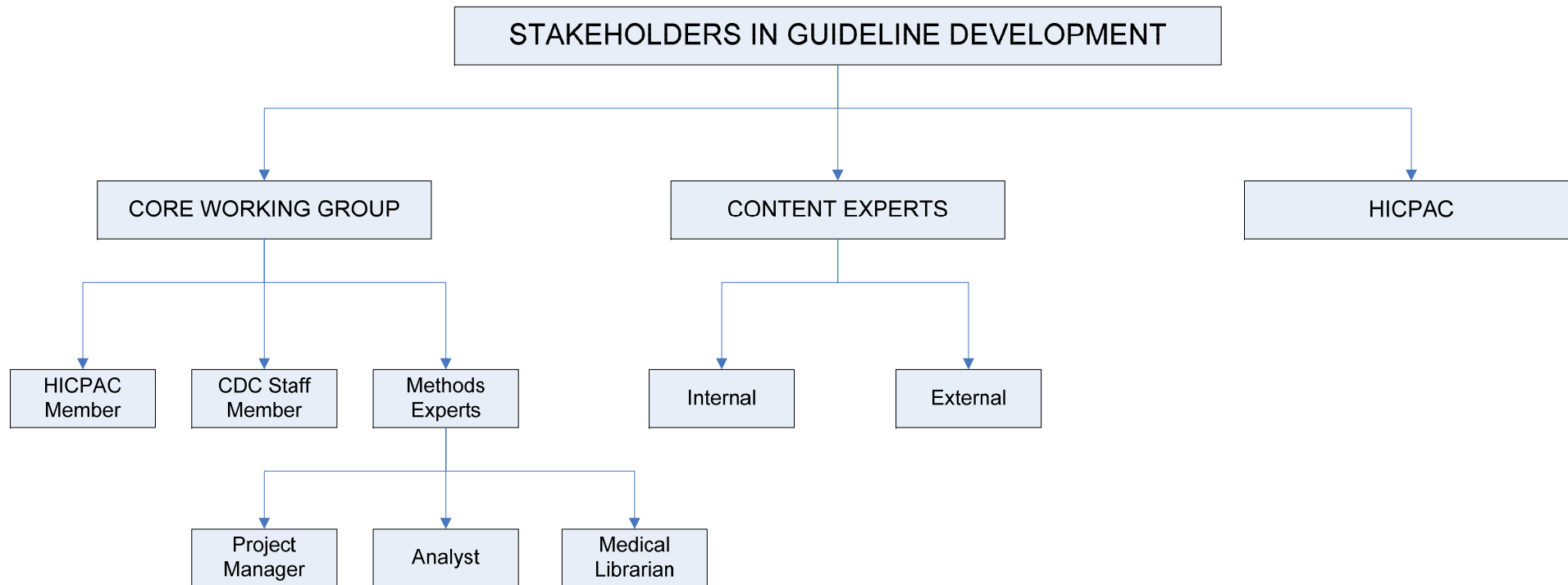
**Table 2: Formulating Recommendations**

<b>HICPAC Recommendation</b>	<b>Weighing Benefits and Harms for Critical Outcomes</b>	<b>Quality of Evidence</b>
STRONG (Category I)	Interventions with net benefits or net harms	Category IA – High to Moderate
		Category IB – Low to Very Low (Established Practice)
		Category IC – High to Very Low (Regulatory)
WEAK (Category II)	Interventions with trade offs between benefits and harms	High to Very Low
No recommendation/unresolved Issue	Uncertain trade offs between benefits and harms	Low to Very Low

**Table 3. Updated HICPAC Categorization Scheme for Recommendations**

Category IA	A strong recommendation supported by high to moderate quality evidence suggesting net clinical benefits or harms.
Category IB	A strong recommendation supported by low quality evidence suggesting net clinical benefits or harms, or an accepted practice (e.g., aseptic technique) supported by low to very low quality evidence.
Category IC	A strong recommendation required by state or federal regulation.
Category II	A weak recommendation supported by any quality evidence suggesting a trade off between clinical benefits and harms.
No Recommendation	An unresolved issue for which there is low to very low quality evidence with uncertain trade offs between benefits and harms.

**Figure 1. Stakeholders in HICPAC Guideline Development**



**Figure 2. The Guideline Development Process**

